Abstracts

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Fifty Percent Area Reduction After Four Weeks of Treatment is a Reliable Indicator for Healing—Analysis of a Single-Center Cohort of 704 Diabetic Patients

Coerper S, Beckert S, Kuper MA, et al. J Diabetes Complications 2009;23: 49-53.

Conclusion: Calculating wound area reduction after 4 weeks is a valid tool to estimate the probability that a diabetic foot wound will heal. A 50% wound area reduction after 4 weeks of therapy indicates likely healing of a diabetic foot wound.

Summary: Subjective and wound-based parameters can be used to document healing of diabetic foot wounds. The only objective wound-based parameters for healing are wound size and ultimate complete wound closure. The authors sought to investigate whether an area reduction >50% with 4 weeks of treatment was associated with long-term probability that a diabetic foot wound would heal.

The authors treated diabetic foot wounds according to an institutional, interdisciplinary wound care protocol. Follow-up was documented using a wound care documentation system and data were analyzed. The probability of healing was assessed with the Kaplan-Meier method, with results expressed as percentage of area reduction. Patients were classified as responders to the protocol when the percentage of wound area reduction reached at least 50% after 4 weeks of treatment, and nonresponders when the percentage area reduction was <50% at 4 weeks. Healing was defined as a percentage area reduction of 100%.

The analyses included 704 patients with a median follow-up of 71 days (range, 2-365 days). Wound duration was 31 days (range, 1-4018 days). Initial wound size was 1.18 cm^2 (range, 0.1-99 cm^2). Bone was involved in the base of the wound in 28%, and in 64.5% both pedal pulses were not palpable. Major amputation rate was 2.8%, and minor amputation rate was 10.2%. Overall probability of healing was 35% after 12 weeks, 41% after 16 weeks, and 73% after 1 year. There were 334 responders (47%) and 370 nonresponders (53%). Responders had a significantly higher probability of healing compared with nonresponders (12 weeks: 52% vs 18%, $P = .0001$; 16 weeks: 47% vs 27%, $P = .0001$; 1 year: 83% vs 65%, $P = .0001$).

Comment: The data suggest that diabetic foot wounds more prone to heal will exhibit a greater healing response early in the course of their treatment. The practical point is that if the wound has not decreased by 50% in area after 4 weeks, an alternative form of wound therapy should be considered.

Plasma Levels of Soluble Tie2 and Vascular Endothelial Growth Factor Distinguish Critical Limb Ischemia from Intermittent Claudication in Patients with Peripheral Arterial Disease

Findley CM, Mitchell RG, Duscha BD, et al. J Am Coll Cardiol 2008;52: 387-93.

Conclusion: VEGF and sTie2 are increased in critical limb ischemia. sTie2 may be a marker and a cause of critical limb ischemia.

Summary: Patients with peripheral arterial disease (PAD) are at increased risk for cardiovascular mortality. Risk is higher for those patients with critical limb ischemia (CLI) vs those with intermittent claudication (IC). The diagnosis of IC vs CLI is, however, purely clinical. In addition, although a lower ankle-brachial index (ABI) is also a marker for increased cardiovascular mortality, ABI does not distinguish between CLI and IC. A potential biomarker that can distinguish between patients with CLI and IC may therefore be useful in risk stratification in patients with PAD.

The authors are expert in fields of angiogenesis, and it is known that alterations in angiogenic growth factors occur in patients with vascular disease. It is, however, unknown whether these growth factors are altered in the subset of cardiovascular disease patients with PAD or whether these potential alterations in growth factors can correlate with the disease severity. In this study the authors therefore sought to determine whether factors that regulate angiogenesis are altered in PAD and if these alternations exist, whether they are associated with PAD severity.

Plasma was collected from 46 patients with PAD (23 with IC and 23 with CLI) and 23 healthy controls. Plasma angiopoietin-2 (Ang2), soluble Tie2 (sTie2), vascular endothelial growth factor (VEGF), soluble VEGF receptor 1 (sVEGFR-1), and placenta growth factor (PlGF) were measured from the plasma samples. In vitro studies of endothelial cells were also performed with recombinant VEGF to investigate effects on sTie2 production.

Concentrations of sTie2 ($P < .01$), Ang2 ($P < .001$), and VEGF ($P < .01$) were significantly greater in PAD patients compared with controls. No differences were found in PlGF or sVEGFR-1. Plasma Ang2 was increased in both IC and CLI patients compared with controls ($P < .0001$). There were no differences in levels in patients with IC and CLI. Plasma levels of sTie2 and VEGF were similar in controls and patients with IC, but were increased in patients with CLI ($P < .001$ vs control or IC). Increased sTie2 and VEGF were independent of ABI or standard cardiovascular disease risk factors. Treatment of endothelial cells with VEFG significantly increased sTie2 shedding.

Comment: It is a bit of a stretch to suggest at this time that VEGF and sTie2 have any utility as biomarkers for the large cohort of patients with CLI. If, however, these biomarkers could be used as a predictor of amputation risk in patients with CLI, adjusted for wound size and ABI, that would be useful. The only real conclusion that can come from this study is that plasma levels of sTie2 and VEGF are increased in patients with PAD and are different in those with a clinical diagnosis of CLI vs those with IC. What we really need in the group of patients with CLI is a predictor of short-term amputation risk, and the data here are not sufficient for that degree of risk stratification.

Angina Pectoris is a Stronger Indicator of Diffuse Vascular Atherosclerosis than Intermittent Claudication: Framingham Study

Kannel WB, Evans JC, Piper S, et al. J Clin Epidemiol 2008;61:951-7.

Conclusion: Angina pectoris is a stronger predictor of diffuse atherosclerotic cardiovascular disease than intermittent claudication (IC).

Summary: IC is an accepted marker of the presence of diffuse atherosclerosis and conveys an increased risk for mortality, primarily from cardiovascular causes. Angina pectoris, another condition provoked by exertion, however, is generally regarded only as a hallmark of impending myocardial infarction. As an example, the Rose angina questionnaire, a tool for epidemiologic investigation of angina, has been tested chiefly as a predictor of coronary morbidity and mortality. In this study the authors use population-based data from the Framingham Study between 1949 and 1990 to assess relative predictive values of IC or angina pectoris for a cardiovascular disease event. The data from 1949 to 1990 were used because this was a time when few widespread therapies were in use for prevention of cardiovascular disease events.

The prospective cohort of this study consisted of 5209 men and women from Framingham, Massachusetts, who were aged 28 to 62 years at the time of enrollment from 1948 to 1951. For 36 years of follow-up they have received biennial examinations. The incidence of development of cardiovascular disease in the Framingham participants with angina pectoris or IC was determined relative to a reference sample free of cardiovascular disease. There were 95 cardiovascular disease events in the 186 participants with IC, and 206 in the 413 patients with angina pectoris. Adjusting for sex, age, and risk factors, the proportion of the IC group developing other cardiovascular disease was 34%, and the proportion for the angina pectoris group was 43.4%. Compared with the reference sample, the IC group had a 2.73-fold higher age and sex-adjusted 10-year hazard ratio for cardiovascular disease (95% confidence interval [CI], 2.21-3.38). For angina pectoris, the cardiovascular disease hazard ratio was 3.17 (95% CI, 2.73-3.69). The standard risk factor adjustments cardiovascular disease hazard ratios were more elevated for patients with angina pectoris than for those patients with IC. Excess cardiovascular disease was accounted for by risk factors in 34.8% of those with IC and 9.5% of those with angina pectoris.

Comment: Angina and IC are both hallmarks of diffuse atherosclerotic vascular disease. The data indicate that both impart a twofold to threefold increased risk of cardiovascular disease compared with a reference group. It is interesting that the factors increasing risk for clinical events in other vascular territories are not a product of the shared risk factors of patients with IC and those with angina pectoris. Coexistent risk factors only accounted for about 35% of the cardiovascular risk for IC and 9.5% of the hazard associated with angina pectoris. The mechanism of this somewhat unexpected observation is uncertain. It is important to note the Framingham Study has few African Americans or other minority populations. The data presented, therefore, cannot be generalized to the entire United States population.

General and Abdominal Adiposity and Risk of Death in Europe

Pischon T, Boeing H, Hoffmann K, et al. N Engl J Med 2008;359:2105-20.

Conclusions: Abdominal adiposity and general adiposity are both associated with risk of death. Waist circumference and waist-to-hip ratios, in addition to body mass index (BMI), should be used in assessing risk of death related to adiposity.

Summary: Calculations of BMI have been used to assess the association between adiposity and risk of death. The authors sought to determine whether the distribution of body fat contributes to the prediction of death